


In re Appln. of 08/915,736

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

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Review Article

Medical Progress

PARKINSON'S DISEASE

Second of Two Parts

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PATHOPHYSIOLOGY

The establishment of a model of parkinsonism through the administration of MPTP to nonhuman primates has provided important insights into new therapeutic strategies. A typical parkinsonian syndrome develops in the animals that is characterized by dopaminergic-cell loss in the substantia nigra and striking abnormalities in the spontaneous activity and sensorimotor responses of neurons in the basal ganglia.^{94,95} A fundamental discovery has been that the dopamine-deficiency state is associated with increased activity of the inhibitory γ -aminobutyric acid (GABA)—employing (GABAergic) output nuclei in the basal ganglia, the internal segment of the globus pallidus, and the pars reticulata of the substantia nigra (Fig. 3). The heightened action of the last two structures is thought to arise from at least two mechanisms: reduced inhibition by a "direct" GABAergic connection from the striatum (caudate nucleus and putamen) and excessive excitation through an "indirect" pathway that contains two inhibitory neuronal connections, the first from the striatum to the external segment of the globus pallidus, and the second from that segment to the subthalamic nucleus. The subthalamic nucleus excites the internal segment of the globus pallidus and the pars reticulata of the substantia nigra by means of the neurotransmitter glutamate.

In the striatum, the GABAergic output neurons projecting directly to the internal segment of the globus pallidus and pars reticulata of the substantia nigra contain a predominance of D1 dopamine receptors, whereas D2 receptors predominate on neu-

rons projecting to the external segment of the globus pallidus. Dopamine has different effects on these receptors and, therefore, on the subpopulations of striatal output neurons, exciting those expressing D1 receptors (the origin of the direct striatopallidal pathway) and inhibiting those with D2 receptors (the origin of the indirect striatopallidal pathway). Figure 3A illustrates the balance of activity between the direct and indirect pathways acting on the internal segment of the globus pallidus and pars reticulata of the substantia nigra in the normal, non-dopamine-deficient state. As shown in Figure 3B, dopamine deficiency (e.g., in MPTP toxicity and Parkinson's disease) causes overactivity of the indirect pathway, resulting in excessive glutamatergic drive to the internal segment of the globus pallidus and pars reticulata of the substantia nigra and reduced activity of the inhibitory GABAergic direct pathway, further disinhibiting the activity of the internal segment of the globus pallidus and pars reticulata of the substantia nigra. Because these structures use the inhibitory neurotransmitter GABA, the increased output of the basal ganglia leads to excessive inhibition and, effectively, to a shutdown of the thalamic and brain-stem nuclei that receive their outflow (Fig. 3B).

The excessive thalamic inhibition leads to suppression of the cortical motor system, possibly resulting in akinesia, rigidity, and tremor, whereas the inhibitory descending projection to brain-stem locomotor areas may contribute to abnormalities of gait and posture. Studies with positron-emission tomography have shown that the reversal of akinesia with dopaminergic drugs is associated with an increase in the activity of the abnormally depressed supplementary motor and premotor cortex,⁹⁶ areas involved in the initiation of movement. This observation suggests that dopamine may reduce the excessive inhibitory outflow from the output nuclei in the basal ganglia. Indeed, the high firing rate of the internal segment of the globus pallidus in both primates given MPTP⁹⁴ and patients with Parkinson's disease⁹⁷ diminishes with the administration of the potent D1 and D2 dopamine-receptor agonist apomorphine in doses that reverse parkinsonism.⁹⁸

The model of the circuitry of the basal ganglia (Fig. 3A and 3B) as originally proposed^{99,100} has a number of deficiencies, however. First, it is incomplete. Often not included and rarely discussed are the other projections from the external segment of the globus pallidus, including direct inhibitory connections to the internal segment of the globus pallidus and the reticular nucleus of the thalamus,^{101,102} the projections from the centromedian and parafas-

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cicular thalamic nuclei to the striatum, the role of direct cortical projections to the subthalamic nucleus, and the role of dopamine outside the striatum, including projections to the subthalamic nucleus and the internal segment of the globus pallidus. The model best accounts for akinesia, but the explanations for rigidity and tremor are less clear.

Two important problems with the model relate to the predicted results of surgical interventions. The model predicts that thalamotomy, with its consequent diminution of thalamic activation of the cortex, should worsen Parkinson's disease and that pallidotomy at the internal segment of the globus pallidus, by diminishing inhibitory outflow from the basal ganglia, should produce hemiballism, as occurs with spontaneous lesions in the subthalamic nucleus. Neither of these predictions is borne out by surgical experience. Indeed, thalamotomy is highly effective in the control of tremor in Parkinson's disease,¹⁰³ and pallidotomy strikingly eliminates dyskinesia induced by levodopa.¹⁰⁴ These inaccurate predictions of surgical response may reflect the fact that the model considers only neuronal discharge rates, rather than the more complex and potentially more important neuronal firing patterns, or the fact that the circuit may behave in a manner different from that expected in the chronic dopamine-deficient state. Despite these deficiencies, this model of the circuitry of the basal ganglia has allowed the generation of hypotheses of the pathophysiology of parkinsonism and its response to treatment that can be tested.

TREATMENT

The management of Parkinson's disease can be subdivided into three categories: protective or preventive treatment, symptomatic treatment, and restorative or regenerative treatment.

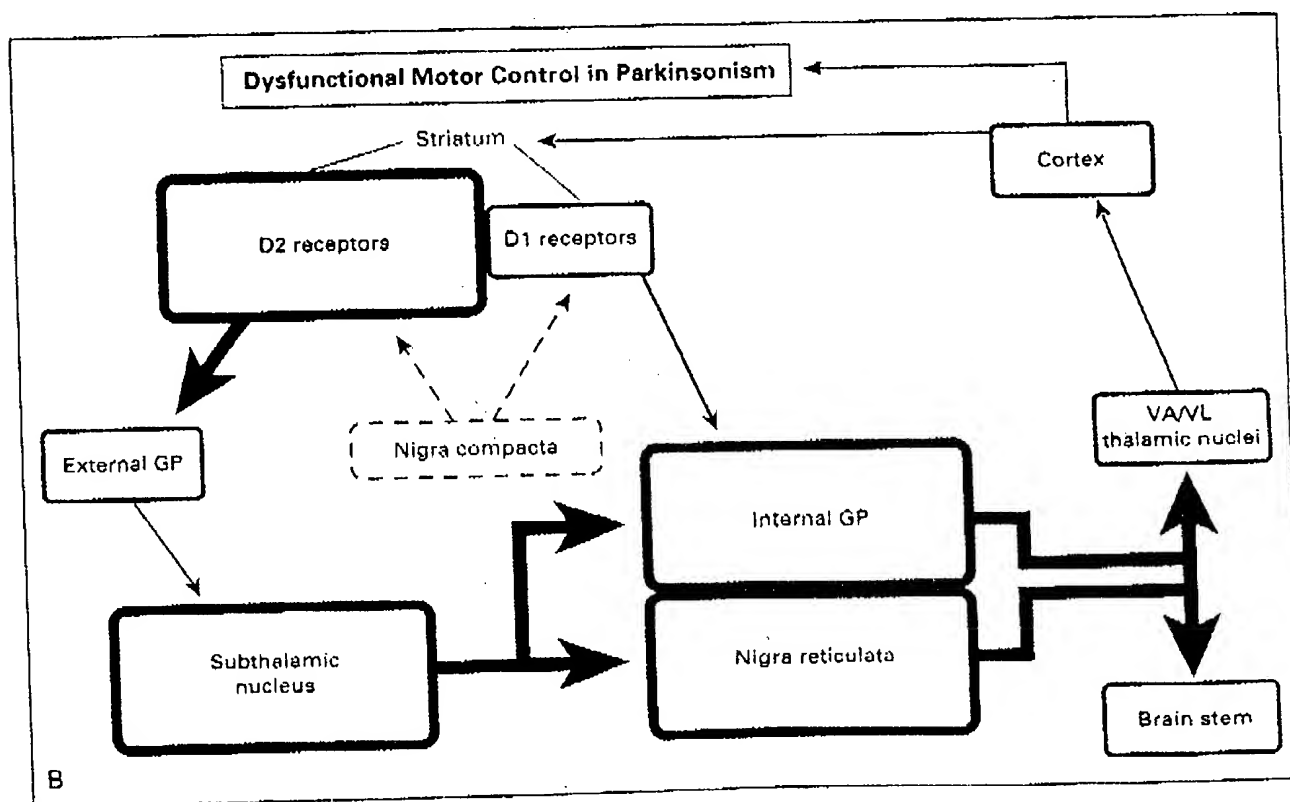
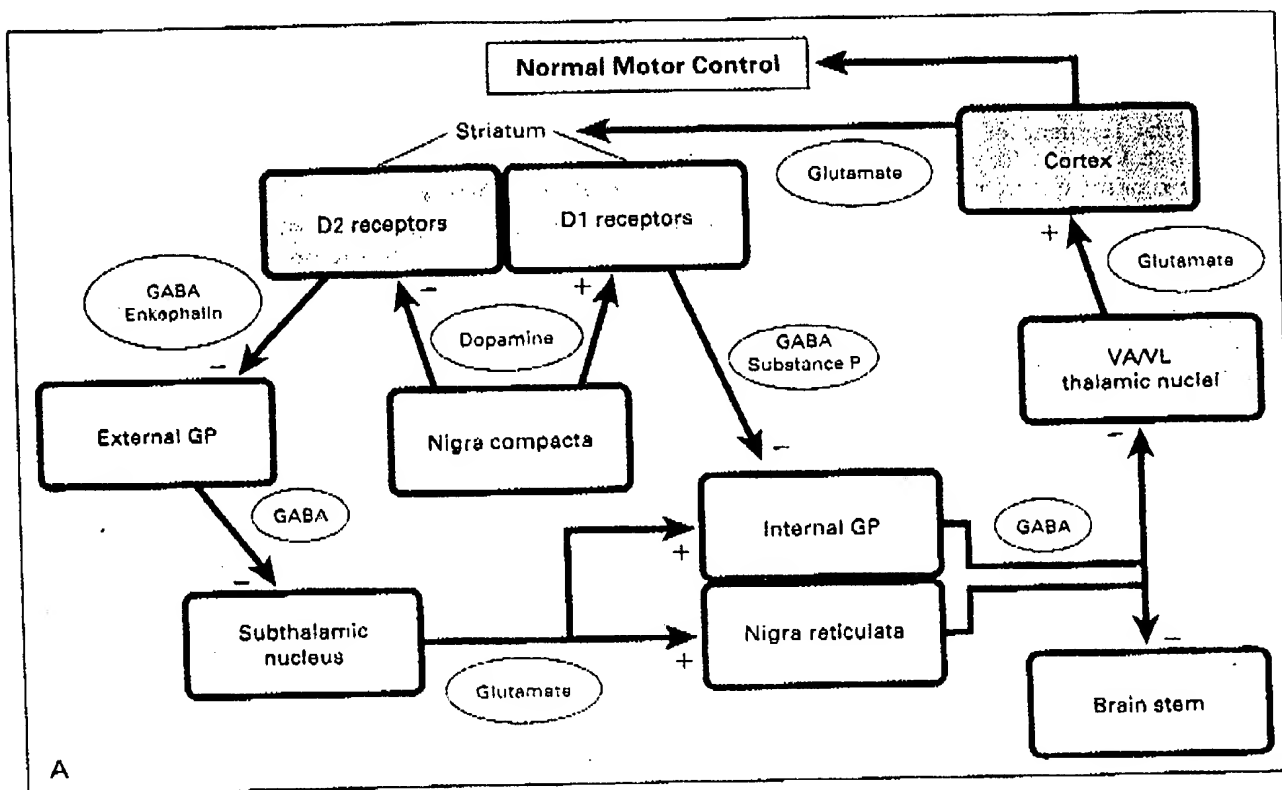
Protective Therapy

None of the currently available treatments have been proved to slow the progression of Parkinson's disease. Although it was initially believed that the selective monoamine oxidase B (MAO-B) inhibitor selegiline delayed the onset of disability requiring therapy with levodopa by slowing the progression of the disease, it is now thought that much of this effect was due to the amelioration of symptoms.¹⁰⁵ In addition, the initial effects were not sustained,¹⁰⁶ and selegiline did not delay the development of dyskinesias or fluctuations in response to levodopa.¹⁰⁷ High doses of the antioxidant vitamin E were ineffective in slowing the progression of the disease. Further studies continue to suggest that selegiline is neuroprotective,¹⁰⁸ and recent studies indicate that it can block apoptosis through a transcriptional effect of its desmethyl derivative that is unrelated to MAO-B inhibition.¹⁰⁹ However, a study in the United Kingdom found significantly higher mortality among patients treated with selegiline plus levodopa than among those treated with levodopa alone.¹¹⁰ This study raises questions about the use of selegiline in Parkinson's disease; however, other experience, including follow-up of the large cohort in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

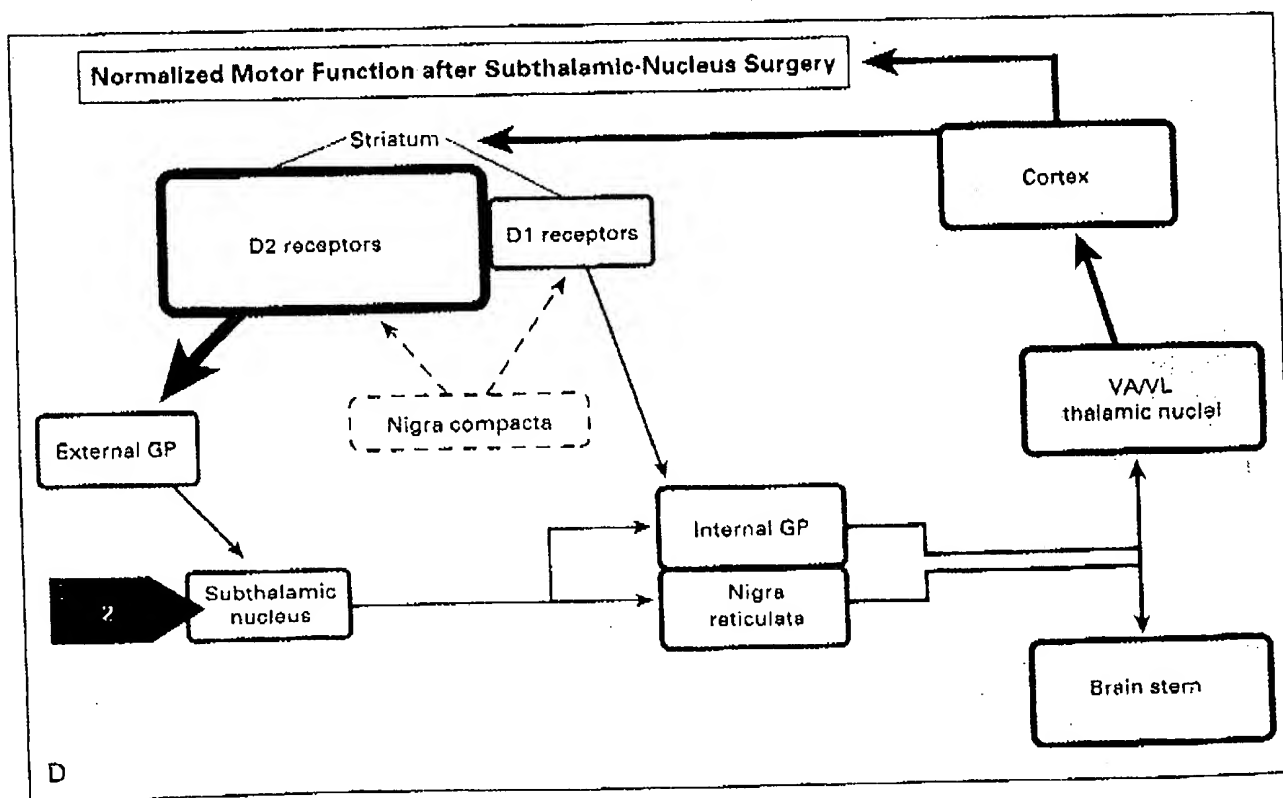
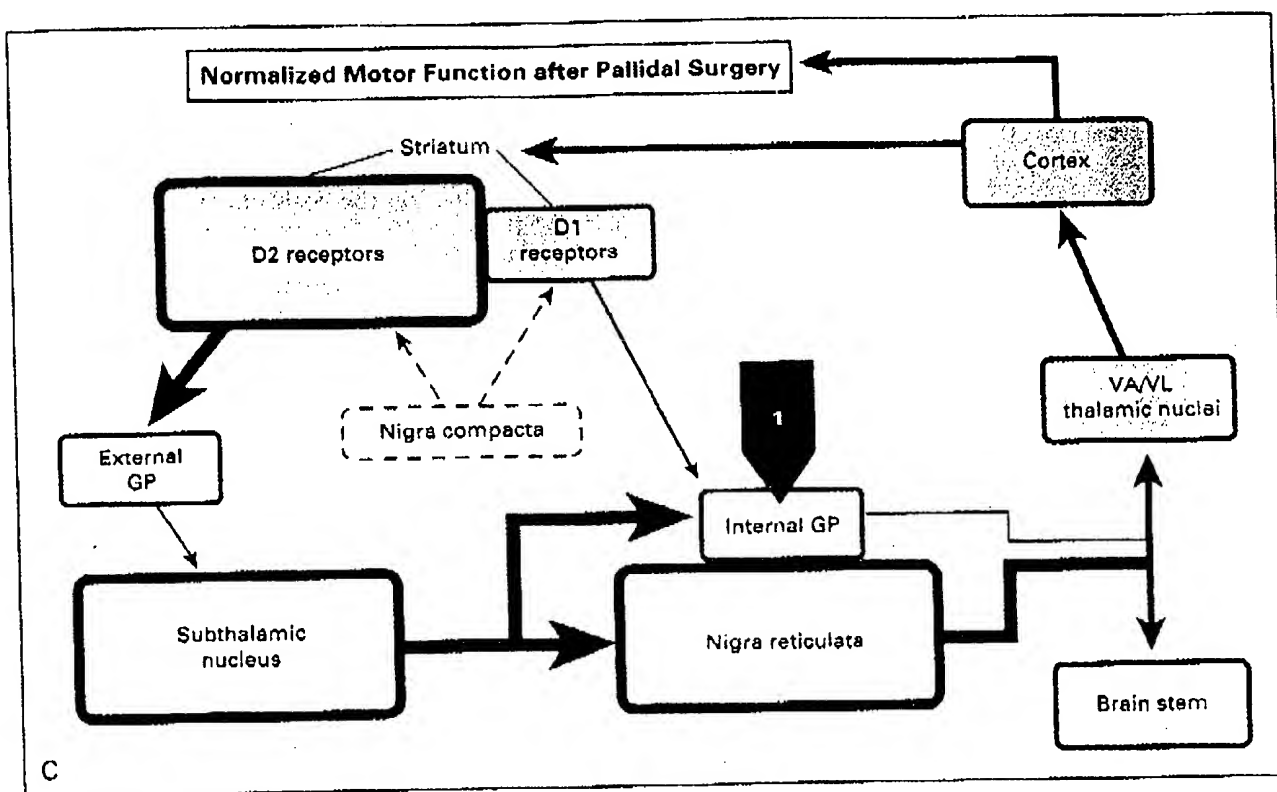
Figure 3 (following pages). Proposed Functional Model of the Basal Ganglia in Persons with Normal Motor Control (Panel A), Patients with Parkinsonism (Panel B), and Patients in Whom Motor Function Has Been Improved by Surgical Interventions in the Medial Globus Pallidus (Panel C) or the Subthalamic Nucleus (Panel D).

For the purposes of clarity, the neuroanatomy and interconnections shown are incomplete. Green arrows indicate excitatory pathways, and red arrows inhibitory pathways. In Panels B, C, and D, the width of the arrows indicates the degree of overall functional change in the activity of each pathway (changes in neuronal firing rates) as compared with the normal state (Panel A), and the size and outlining of each box indicate the activity of the brain region as compared with the normal level of activity (Panel A). Dashed lines and arrows indicate the dysfunctional nigrostriatal dopamine system in Parkinson's disease. The circled substances are neurotransmitters used by the neighboring pathway. The brain stem as depicted includes the pedunculopontine nucleus, and the cortex includes supplementary motor areas and premotor cortex. D1 receptors denotes neurons containing predominantly D1 dopamine receptors, D2 receptors neurons containing predominantly D2 dopamine receptors, nigra compacta the pars compacta of the substantia nigra, external GP the external portion of the globus pallidus, internal GP the internal portion of the globus pallidus, nigra reticulata the pars reticulata of the substantia nigra, VA/VL ventral anterior and ventrolateral, and GABA γ -aminobutyric acid. The 1 indicates a lesion or high-frequency stimulation in the internal segment of the globus pallidus, and the 2 high-frequency stimulation or lesion in the subthalamic nucleus. Plus signs indicate excitation, and minus signs inhibition.

Alterations in firing patterns in Panels B, C, and D (e.g., more bursting or irregular patterns of discharge, as compared with continuous or tonic firing in the normal state) may have an important functional role that is poorly understood at present. Parkinsonism (Panel B) is associated with increased inhibition of the motor thalamus (and, as a result, premotor cortexes) and brain-stem locomotor areas resulting from overactivity of the internal segment of the globus pallidus and pars reticulata of the substantia nigra. The excessive activity of these two areas is due to reduced direct inhibition from the striatum and especially to excessive stimulation from the overactive subthalamic nucleus. An increase in dopaminergic action at the level of the striatum due to drug therapy (e.g., levodopa or dopamine agonists) would partially reverse this state (not shown). Surgically reducing the activity of the internal segment of the globus pallidus (Panel C) would also partially reverse this state by eliminating the excessive inhibition due to this component of the output of the basal ganglia. On the other hand, reducing the excessive excitatory activity of the subthalamic nucleus (Panel D) would have the advantage of reducing the overactivity of both components of the output of the basal ganglia, the internal segment of the globus pallidus, and the pars reticulata of the substantia nigra.



MEDICAL PROGRESS



study, has not shown higher mortality among patients treated with selegiline.¹¹¹⁻¹¹³

As outlined earlier in this review, the causes and pathogenesis of Parkinson's disease are unknown. The development of effective protective therapy will require advances in our understanding of the disease. As new drugs become available, treatments that influence oxidative phosphorylation and damage due to free radicals, excessive iron deposition, disturbances of calcium homeostasis, cytokines, excitotoxicity, nitric oxide, apoptosis, and the products of causative genes may all be considered in attempts to provide effective neural protection.

Symptomatic Therapy

Early Medical Treatment

Levodopa remains the most effective treatment for Parkinson's disease. However, levodopa is associated with a number of problems. There has been extensive debate about when to begin levodopa therapy. The controversy relates to the widely held beliefs that levodopa has an important benefit for only five to seven years and that patients thereafter lose their response to the drug; that early use of levodopa results in the earlier development of complications such as motor fluctuations ("wearing-off" and "on-off" phenomena, defined below) and dyskinesias; and finally, that levodopa may be toxic — possibly because it increases dopamine turnover, with the formation of oxygen free radicals and peroxynitrite — and may thereby speed the progression of Parkinson's disease.¹¹⁴ The first belief is patently false. With time, certain symptoms develop that may be resistant to levodopa (Table 3), but most patients, if not all, continue to derive a substantial benefit from levodopa over the entire course of their illness. Although the response later in the course of the disease is often complicated by additional problems, it is generally believed that the later-stage motor complications (Table 3) are related to the severity of the underlying disease as well as to treatment-related factors such as the duration and dose of levodopa therapy. In patients in whom therapy with levodopa has been delayed, often unnecessarily, until pronounced disability is present, motor complications often develop much more rapidly than in patients treated earlier in the course of their illness.

Finally, the emphasis on the toxic potential of levodopa has been strongly criticized recently.¹¹⁷ There are no convincing experimental or clinical data that show that levodopa accelerates the neurodegenerative process, and in fact, some studies even suggest a neurotrophic effect. Levodopa increases life expectancy among patients with Parkinson's disease, and it has recently been shown that survival is significantly reduced if administration of the drug is delayed until greater disability with impaired postural reflexes develops.¹¹⁸

Therefore, early treatment should be guided by the goal of providing maximal comfort and improved quality of life while limiting reversible but long-term side effects. Treatment intended to delay the introduction of levodopa should be used in an attempt to forestall the development of these side effects rather than on the basis of concern about toxicity or the hope of delaying the optimal response until greater disability develops.

Drugs such as anticholinergic agents, amantadine, and selegiline provide only mild-to-moderate benefit. Eventually, levodopa or dopamine agonists are required for progressive disability. However, dopamine agonists may provide inadequate benefit, usually take longer than levodopa to reach effective doses, and have always required that supplementary levodopa be given for supervening disability after varying periods of time. Most long-term studies of dopamine-agonist monotherapy in patients with previously untreated Parkinson's disease have involved bromocriptine. Approximately one third of such patients have good responses to this drug, and some may not require levodopa for two to five years. Typically, patients treated with dopamine agonists alone do not have fluctuations and dyskinesias until levodopa is added to the regimen to treat supervening disability.¹¹⁹ Although the newer dopamine agonists, pramipexole,¹²⁰ ropinirole,¹²¹ and cabergoline,¹²² have all been shown to have benefit in previously untreated patients, it is unknown whether they will prove to have better long-term efficacy with fewer complications than bromocriptine or pergolide.

One reason that dopamine agonists infrequently result in fluctuations and dyskinesias may be their longer duration of action, which more closely mimics the physiologic tonic release of dopamine from normal nigral neurons, in contrast to the pulsatile stimulation of receptors caused by intermittent doses of standard levodopa formulations.¹²³ A five-year study comparing regular levodopa and carbidopa with a controlled-release formulation in patients with early Parkinson's disease found no difference in the rates of dyskinesias and fluctuations in the two treatment groups. However, the incidence of these complications was surprisingly low in both groups.¹²⁴

Problems in Later Medical Treatment

Early on, the response of the major symptoms in patients with Parkinson's disease may be inconsistent. Tremor, especially, may be more resistant to medical therapy than other symptoms. The reasons for this variable response are not known; however, pathologic involvement of nondopaminergic areas of the brain may be one explanation. Certainly this is an important explanation for many of the nonmotor symptoms and the later-stage levodopa-resistant motor disturbances. The latter largely account for the persistent and progressive disability in the "on" pe-

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TABLE 3. PROBLEMS AND COMPLICATIONS OF LEVODOPA THERAPY.

PROBLEM	SYMPTOMS
Related to disease	
Early suboptimal symptom control	Varying response of symptoms to treatment Greater resistance of tremor than of other symptoms
Later treatment-resistant symptoms	
Motor	Dysarthria Freezing of gait (on-period freezing) Postural instability with falls Dysautonomia, weight loss
Nonmotor*	Sensory symptoms including pain (some may be responsive to levodopa) Changes in mood or behavior, sleep disturbances Cognitive dysfunction and dementia
Related to treatment and disease	
Motor fluctuations	Wearing off of drug effect (end-of-dose deterioration), concomitant fluctuations of nonmotor symptoms that may be as disabling as motor symptoms (or more so) ¹¹⁸ On-off phenomenon, more rapid and unpredictable fluctuations Peak-dose dyskinesias: chorea, athetosis, and less often, more prolonged dystonia, often worse on initially affected side Diphasic dyskinesia ("beginning-of-dose" and "end-of-dose" dyskinesias), mixtures of choreoathetosis, ballism, dystonia, alternating movements (especially in legs) Off-period dystonia, most often involving legs and feet (including morning foot dystonia)
Dyskinesias (abnormal involuntary movements)	Vivid dreams and nightmares Rapid-eye-movement sleep behavior disorder (may develop before parkinsonism ¹¹⁹) Visual hallucinations with clear sensorium Hallucinations with confusion Mania, hypersexuality Paranoid psychosis
Psychiatric disturbances	

*These symptoms sometimes occur earlier in the course of the illness.

riods (those characterized by greater mobility due to the beneficial actions of levodopa) of motor fluctuations.¹²⁵ Motor fluctuations occur in approximately 50 percent of patients after 5 years of levodopa therapy (at this time they usually affect patients for less than 25 percent of their waking hours), and the proportion of patients affected increases to 70 percent among those treated for more than 15 years.¹²⁶ Such fluctuations are more common among patients with young-onset Parkinson's disease.¹²⁷ Motor complications include predictable "off" periods (predictable periods of immobility or greater severity of other parkinsonian symptoms when medications wear off — i.e., "wearing off"), unpredictable off periods (or on-off fluctuations), and various forms of abnormal involuntary movements.

Wearing off can be defined as a perception of loss of mobility or dexterity, usually taking place gradually over a period of minutes (up to an hour) and usually having a close temporal relation to the timing of antiparkinsonian medications. On-off effects are unpredictable and generally sudden occurrences (lasting seconds to minutes) of shifts between on and off periods that are not apparently related to the timing of antiparkinsonian medication. These off

periods last minutes to hours and do not include transient episodes of "freezing" (also referred to as "motor blocks"; the initiation or continuation of a motor act such as walking is arrested for a few seconds) or stress-induced tremor, which are both components of the underlying disease and occur even in the absence of treatment.

As the disease progresses, failing endogenous synthesis and capacity for storage of dopamine result in greater evidence of the so-called short-duration response to levodopa, manifested by obvious dose-related improvement in symptoms that lasts for minutes to hours and is followed by a return of parkinsonism as the dose wears off. In addition, "negative responses," which are brief periods of worsening of symptoms immediately before and after the short-duration response, may accentuate the patient's awareness of motor fluctuations.¹²⁸ In addition to presynaptic changes in the nigrostriatal dopaminergic system, postsynaptic changes — for example, in the striatum and its projections to the globus pallidus¹²⁹ — possibly involving altered glutamatergic responses may also contribute to the shorter duration of the effects of levodopa. This possibility is supported by the observation of a similar decline in the duration of effect

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TABLE 4. DRUGS FOR PARKINSON'S DISEASE.

CLASS	DRUG	USUAL FINAL DOSAGE	IMPORTANT ADVERSE EFFECTS*	COMMENTS
Anticholinergic	Many (e.g., benztropine, trihexyphenidyl)	Varied	Peripheral (e.g., dry mouth, blurred vision, constipation, difficulties with urination); central (confusion, memory problems, hallucinations)	Relatively contraindicated in elderly and contraindicated in patients with cognitive disturbances
Miscellaneous	Amantadine	100 mg 2 or 3 times/day	Confusion, visual hallucinations; livedo reticularis, swelling of ankles; dose reduction or drug withdrawal necessary in the presence of renal failure	Previously considered a dopaminergic drug, now thought to act primarily through NMDA-antagonist effects; dyskinesias often improve with treatment
Dopamine precursor	Levodopa Given with peripheral dopa decarboxylase inhibitor (carbidopa [in 4:1 and 10:1 ratios] or benserazide [4:1]†) Controlled-release formulations (with carbidopa [4:1] or benserazide [4:1]†)	Varied; begin with 3-times-daily schedule (controlled-release levodopa-carbidopa may be given twice daily at first); late in disease patients may require multiple doses/day (sometimes >2 g/day), with meals avoided in order to improve absorption	Peripheral and central dopaminergic side effects: peripheral (e.g., nausea, vomiting, and orthostatic hypotension); central (i.e., motor fluctuations, dyskinesias, psychiatric disturbances)	Peripheral side effects often controlled by additional carbidopa or the peripheral dopamine-receptor blocker domperidone†
Dopamine agonist	Ergot-derived Bromocriptine	30 to 40 mg/day	Peripheral and central dopaminergic side effects; pedal edema Pleuropulmonary reaction, retroperitoneal fibrosis, erythromelalgia	Peripheral side effects often well controlled with domperidone† Rare pulmonary, retroperitoneal, and skin effects possibly due to ergot derivation (drug withdrawal usually required)
	Pergolide	3 to 5 mg/day	As for bromocriptine	As for bromocriptine
	Cabergoline†	2 to 6 mg/day	As for bromocriptine	As for bromocriptine Long half-life allows once-daily dosage
Non-ergot-derived	Lisuride†	2 to 5 mg/day	As for bromocriptine	As for bromocriptine
	Ropinirole	Up to 24 mg/day in 3 divided doses	Similar peripheral and central dopaminergic side effects to those of ergot-derived dopamine agonists, with the probable exceptions of pleuropulmonary reaction, retroperitoneal fibrosis, and erythromelalgia	Effective as first-line and adjunctive therapy; dopamine D3-agonist effects could contribute to efficacy
	Pramipexole	Up to 4.5 mg/day in 3 divided doses	As for ropinirole	As for ropinirole, possibly greater "D3-preferring" effects; may be neuroprotective
	Apomorphine	Parenteral agent as needed or given as continuous infusion	Peripheral and central dopaminergic side effects Local skin reactions including nodule formation	Concomitant antiemetic (e.g., domperidone,† trimethobenzamide) needed
Monoamine oxidase B inhibitor	Selegiline	5 mg 2 times/day	Dopaminergic effects of other drugs possibly accentuated, insomnia, confusion	Last dose given at mid-day

of the direct-acting dopamine agonist apomorphine, which cannot be explained by alterations in the integrity of presynaptic dopamine neurons.^{129,130}

Rapid and unpredictable fluctuations develop as the response to levodopa becomes less graded, with small changes in concentration producing large changes in response.¹²⁸ At this stage, there is also a potentially important contribution of pharmacokinetic factors such as the unpredictable absorption and transport of levodopa across the blood-brain barrier. An increase in the interval between a dose of medication and the patient's experience of an on response ("delayed on") and the absence of a response

to an individual dose ("dose failure" or "no on") may relate to delayed gastric emptying.¹³¹ In these situations, patients may notice that their medication takes much longer to have an effect than it used to and that sometimes it does not seem to work at all.

Levodopa-induced dyskinesias are clinically and pharmacologically heterogeneous.^{132,133} Dystonic posturing of a limb is usually the effect of a critically low level of dopaminergic stimulation, typically occurring in the off periods. Many patients, especially early in the course of disease, are unaware of the presence of their choreoathetotic movements, which usually occur when the effect of the medication is at its peak.

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TABLE 4. CONTINUED.

CLASS	DRUG	USUAL FINAL DOSAGE	IMPORTANT ADVERSE EFFECTS*	COMMENTS
Catechol O-methyltransferase inhibitor	Tolcapone	100 or 200 mg 3 times/day (at 6-hr intervals)	Effects of levodopa accentuated, diarrhea in approximately 5% of patients	Dose of levodopa may have to be reduced by as much as 25%; diarrhea (sometimes explosive) typically forces discontinuation; liver-function tests required at base line and every 6 weeks for the first 6 months
Atypical neuroleptic	Entacapone†	200 mg 4 to 10 times/day (given with levodopa)	As for tolcapone	As for tolcapone; diarrhea possibly less frequent
	Clozapine	Wide range (6.25 to 150 mg/day), usually <75 mg/day	Agranulocytosis, sedation, hypotension, sialorrhea	Very low risk of worsening parkinsonism, agranulocytosis rare (<1%) and reversible if discovered early (requires weekly monitoring of complete blood count); may improve other symptoms such as tremor, ¹⁴⁷ akathisia, dyskinesias ¹⁴⁸
	Risperidone	Up to 1.5 mg/day	Worsening of parkinsonism (due to D2-receptor-blocking effects); other neuroleptic effects	Lower risk of extrapyramidal effects than with standard neuroleptics but not as low as with clozapine
	Olanzapine	0.5 to 15 mg/day ¹⁴⁹	As for risperidone; possibly less risk of increasing parkinsonism	Possibly as for risperidone
	Quetiapine	25 to 150 mg/day ¹⁵⁰	As for olanzapine	Possibly as for risperidone

*Central effects are listed in Table 3.

†This drug or formulation is unavailable in the United States.

With time, these dyskinesias may become a source of considerable disability and may persist throughout the response to an individual dose ("square-wave dyskinesias," which start abruptly when the on period begins and subside when the off period develops). Some patients have enhanced dyskinesia, especially involving the lower body, at the onset or end of the response to medication (so-called diphasic dyskinesias).

The pathophysiologic bases of the various types of dyskinesia remain uncertain. The roles of different subclasses of dopamine receptors (D1 and D2), the differing activities of the indirect and direct striatopallidal pathways, and the influence of other transmitters (e.g., GABA, enkephalin, and especially, glutamate^{134,135}) remain controversial.^{136,137} As discussed above, the pharmacodynamic alteration in the signal-transduction mechanisms of striatal output neurons that contribute to these complications may be due, in part, to the nonphysiologic, pulsatile stimulation of dopamine receptors that results from the short half-life of standard levodopa preparations.¹³⁸ This hypothesis is supported by the progressive improvement in fluctuations, including dyskinesias, in the response to treatment in patients treated with continuous methods of dopaminergic stimulation, such as intravenous or intraduodenal levodopa infusions^{139,140} and apomorphine or lisuride pumps.^{141,142}

The psychiatric complications of therapy with levodopa and other dopaminergic drugs are also var-

ied and complex (Table 3). Preexisting cognitive dysfunction predisposes patients to some of these problems. The presence of hallucinations is the strongest predictor of subsequent placement in a nursing home,¹⁴³ and mortality is clearly increased among such patients.¹⁴⁴ It has been generally believed that psychiatric complications are due to the stimulation of dopamine receptors outside the motor striatum—for example, in the mesolimbic and mesocortical dopamine systems. The role of the D4 subclass of dopamine receptor is emphasized by evidence of the clinical efficacy of the atypical neuroleptic drug clozapine.¹⁴⁵ However, other nondopaminergic neurotransmitters, particularly the serotonin system, may also have a role.¹⁴⁶

Management of Late-Stage Problems

A detailed discussion of the management of late-stage problems in Parkinson's disease is beyond the scope of this review. Brief general recommendations will be given here. Table 4 provides information on the drugs currently or soon to be available for the treatment of Parkinson's disease. When a patient has an inadequate response to the peak effect of levodopa, it is important to review the accuracy of the diagnosis (Table 1) and to ask whether the target symptoms are typically levodopa-resistant (Table 3). Levodopa-resistant symptoms, more often seen in patients with long-standing disease, can sometimes worsen paradoxically in response to higher doses of

levodopa or dopamine agonists (e.g., on-period freezing of gait, falling, or dysarthria). A cautious trial of a lower dose of these drugs should therefore be considered. Speech, physiotherapy, and occupational therapy all play an important part in managing some of these motor problems. Surgery (discussed below) may be useful for drug-resistant tremor, but the role of surgery in managing other levodopa-resistant problems is controversial, and to date there are no convincing reports demonstrating a benefit.

The wearing off of the effect of drugs can be managed in a variety of ways, including more frequent doses of standard levodopa, the use of controlled-release levodopa (which has lower bioavailability than the standard drug and therefore often requires an increase in total dosage), the addition of a dopamine agonist, and the use of a drug designed to extend the duration of the response to levodopa by reducing the metabolism of levodopa, dopamine, or both. The drugs in the last category include the MAO-B antagonist selegiline and the new catechol O-methyltransferase inhibitors, tolcapone and entacapone. Catechol O-methyltransferase inhibitors prolong the action of an individual dose of levodopa and significantly reduce off time, although increased dyskinesias or induction of hallucinations may require a reduction in the dose of levodopa.^{151,152} Severe, unpredictable fluctuations, which are usually accompanied by problematic dyskinesias, are exceedingly difficult to manage.

In addition to the approaches just mentioned, hourly intake of a liquid preparation of levodopa¹⁵³ or, where available, parenteral apomorphine or lisuride given either as needed or by constant infusion, may be extremely effective.^{141,142} "Delayed-on" and dose failures may improve in response to agents that promote gastric motility, such as cisapride¹⁵⁴ or duodenal infusions of levodopa, which are delivered directly to the sites of absorption in the small bowel.¹⁴⁰ Peak-dose and square-wave dyskinesias may improve in response to a lower dose of levodopa; however, more frequent smaller doses may cause more off time and dose failures.¹⁵⁵ Occasionally, the use of high doses of a dopamine agonist combined with very low doses of levodopa will improve severe fluctuations and dyskinesias. Disabling dyskinesias are often resistant to currently available treatments. Propranolol,¹⁵⁶ fluoxetine,¹⁵⁷ clozapine,¹⁵⁸ and buspirone¹⁵⁹ are occasionally effective. Amantadine may reduce dyskinesia,¹⁶⁰ possibly by NMDA-antagonist effects. Studies in animals suggest that newer glutamate antagonists may be very effective in controlling peak-dose dyskinesias.¹³⁵ Patients with painful off-period dystonia that persists despite treatments designed to reduce fluctuations may benefit from baclofen, lithium, or injections of botulinum toxin. All forms of dyskinesia, as well as disabling off-period symptoms, may respond to surgical therapy.

Depression in patients with Parkinson's disease is treated in the same way as depression in those without Parkinson's disease; patients are often elderly and therefore more susceptible than younger persons to the anticholinergic effects of certain tricyclic antidepressants. There is theoretical concern about the use of selective serotonin-reuptake inhibitors because of their potential to worsen parkinsonism¹⁶¹ and to interact adversely with selegiline.¹⁶²

When visual hallucinations are present, it is important to rule out a systemic illness such as a concurrent infection or metabolic disturbance. The drugs with low ratios of therapeutic to toxic effects should then be eliminated; these include anticholinergic drugs, amantadine, and selegiline. The dose of the dopamine agonist and then levodopa should be reduced to the minimum necessary for optimal clinical control. Catechol O-methyltransferase inhibitors could be discontinued either before or after adjustment of the dose of the dopamine agonist, but before the dosage of levodopa is altered. If hallucinations are mild, infrequent, and nonthreatening, one can then monitor the patient closely.

In the case of more severe hallucinations or psychosis, the use of an atypical neuroleptic agent is indicated. At present, the most widely used and effective of these is clozapine.¹⁴⁵ Risperidone often worsens the underlying parkinsonism. The relative safety and efficacy of newer atypical neuroleptics such as olanzapine and quetiapine remain to be determined; certainly, olanzapine is capable of increasing parkinsonism, whereas there are fewer data on quetiapine. Ondansetron, an antagonist of the 5-hydroxytryptamine₂ receptor, may be effective,¹⁴⁶ but its high cost precludes routine use. Electroconvulsive therapy may also be beneficial in patients who are not confused¹⁶³; this treatment also has the potential to improve response fluctuations temporarily. Generally, there is no justification for "drug holidays" (i.e., the temporary complete withdrawal of levodopa),¹⁶⁴ which may be associated with substantial morbidity, including life-threatening symptoms akin to the neuroleptic malignant syndrome.¹⁶⁵

Dementia accompanying Parkinson's disease remains the greatest therapeutic challenge. Currently, there is no proven treatment for this increasingly common problem. Although the newer cholinergic agents used in Alzheimer's disease^{166,167} have not been studied in detail in patients with parkinsonian dementia, the involvement of cortical cholinergic projections suggests that these drugs might have beneficial effects on cognition and behavior in patients with Parkinson's disease. However, there is a strong possibility that they might worsen parkinsonian symptoms by increasing striatal cholinergic activity. Table 5 lists therapies under development, including agents that may be more appropriate for this problem in the future (e.g., neuronal nicotinic agonists).

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TABLE 5. DEVELOPING AND FUTURE TREATMENT APPROACHES FOR PARKINSON'S DISEASE.

CATEGORY	EXAMPLES	COMMENTS
New formulations of levodopa	Levodopa ethyl ester, ¹⁶⁸ levodopa methyl ester	Soluble prodrugs of levodopa given parenterally
Dopamine-transport inhibitors	NS-2214 ¹⁶⁹	Increase endogenous dopamine in synaptic cleft; animal studies show antiparkinsonian effects without dyskinesias; possible neuroprotective effect due to blocking of uptake of toxins into dopaminergic neurons
Monoamine oxidase B inhibitors	Newer formulations of selegiline, lazabemide, ¹⁷⁰ rasagiline	Designed to bypass first-pass hepatic metabolism (given by transdermal patch, or sublingually); possible neuroprotective or neurotrophic effect
Monoamine oxidase A inhibitors	Muclofenide	Antidepressant; possibly other effects (e.g., neuroprotection)
Dopamine D1-receptor agonists	ABT-431 ¹⁷¹	May reduce dyskinesia as well as improve parkinsonism Longer-acting D1-receptor agonists result in desensitization
Newer methods of drug application	Transdermal patch (N-0923, a D2-receptor agonist ¹⁷²); nasal insufflation and sublingual (apomorphine ¹⁷³)	Current intranasal formulations of apomorphine may cause nasal crusting and vestibulitis
Adenosine A _{2A} antagonists ¹⁷⁴	KW6002	May reduce output of striatal neurons projecting to external segment of globus pallidus (indirect pathway) by increased GABA-mediated feedback inhibition and reduced acetylcholine release
Glutamate antagonists	Remacemide, ¹⁷⁵ dextromethorphan, riluzole	Potentiate effects of levodopa and may reduce dyskinesias ¹⁷⁵ ; possible neuroprotective effect
Neuronal nicotinic-receptor agonists ¹⁶⁷	SIB1508Y, ABT418	Enhance striatal dopamine and release of norepinephrine in cortex and release of acetylcholine in frontal cortex and hippocampus; possible improvement in motor and cognitive disturbances; possible additional neurotrophic effects
Neurotrophic factors	Intraventricular GDNF Neurotrophic immunophilins (GPI-1046) ¹⁷⁶	Striking effects in animal models Striking effects in animal models; active orally, unlike other neurotrophic polypeptides
κ Opioid-receptor agonists	Eradoline, U-69,593	Cause presynaptic reduction in glutamate release; antiakinetic and synergistic with levodopa in animal models ¹⁷⁷

Surgical Therapy and Restorative Therapy

A greater understanding of the pathophysiologic correlates of parkinsonism is largely responsible for the resurgence of functional neurosurgical procedures in the treatment of this disease. The target of such procedures is the disrupted activities of the motor thalamus, the internal segment of the globus pallidus, or the subthalamic nucleus. The introduction of MRI and the use of microelectrode recording techniques have improved the safety and accuracy of functional neurosurgical procedures. Despite reduced surgical morbidity, ablative procedures are still associated with a risk of permanent complications, especially when bilateral lesions are created. For this reason, long-term electrical stimulation through implanted deep-brain electrodes is being studied as a potentially reversible and adjustable treatment method. Although the mechanism through which deep-brain stimulation acts is not understood, the striking similarities in the clinical effects obtained with surgical lesions and

with deep-brain stimulation suggest that long-term electrical stimulation at the levels used clinically acts to disrupt or inhibit neuronal activity.

The proposed model of the function of the basal ganglia (Fig. 3A) and the changes that occur in Parkinson's disease (Fig. 3B) predict that surgical reduction of the excessive inhibitory output of the internal segment of the globus pallidus to the motor thalamus (Fig. 3C) or reduction of the excessive drive of the subthalamic nucleus to both output components of the basal ganglia (internal segment of the globus pallidus and pars reticulata of the substantia nigra) (Fig. 3D) should increase the activation of premotor cortexes and result in a more nearly normal state. The observation that both pallidotomy and deep-brain stimulation of the internal segment of the globus pallidus or subthalamic nucleus cause activation of premotor and supplementary motor areas associated with the reversal of parkinsonism¹⁷⁸⁻¹⁸⁰ is consistent with this view.



Figure 4. Axial T₁-Weighted MRI Scan Showing a Right-Sided Lesion in the Posteromedial Portion of the Globus Pallidus.



Figure 5. T₁-Weighted MRI Scan Showing Bilateral Quadripolar Electrodes Implanted in the Subthalamic Nucleus.

Surgery is reserved for disabling, medically refractory problems. The thalamic target is currently used exclusively for tremor, whereas surgery on the internal segment of the globus pallidus and subthalamic nucleus is being studied for the treatment of all features of parkinsonism, as well as drug-induced dyskinesias. Interventions at the ventrointermediate thalamic nucleus provide approximately 80 percent reductions in contralateral arm tremor.^{103,181,182} However, this effect may not be accompanied by a clinically significant improvement in the ability to perform activities of daily living,¹⁸¹ since resting tremor is often not an important cause of functional disability in Parkinson's disease. Although rigidity may decrease, disabling akinesia is not improved by thalamotomy or thalamic stimulation, and gait dysfunction occasionally increases. Levodopa-induced dyskinesias may also improve, depending on the exact site of the lesion or electrode placement.

Pallidotomy (Fig. 3C and 4) is associated with a striking improvement in levodopa-induced dyskinesias (an improvement of 80 percent or more in contralateral drug-induced dyskinesias), and approximately a 30 percent improvement in total motor scores, with significant reductions in contralateral akinesia, rigidity, and tremor.^{104,183-185} These benefits translate into improvements in the ability to perform activities of daily living and increased independence.¹⁰⁴ Unilateral pallidotomy, however, results in predominantly contralateral motor benefits, and the improvements it produces in gait and postural symptoms may be relatively short-lived — lasting only three to six months, in our experience.¹⁰⁴ Bilateral pallidal procedures have been performed to address these shortcomings. Although there are some reports of a benefit,¹⁸⁶ there is also a greater risk of adverse effects, especially cognitive and bulbar dysfunction. This risk has encouraged the development of deep-brain stimulation as an alternative. Preliminary reports suggest that bilateral deep-brain stimulation of the internal segment of the globus pallidus^{187,188} or, particularly, the subthalamic nucleus¹⁸⁸ (Fig. 3C, 3D, and 5) — as described elsewhere in this issue of the *Journal* by Limousin et al.¹⁸⁹ — can have striking benefits in terms of all aspects of parkinsonism.

Other surgical strategies are at various stages of development. Although surgeons have traditionally avoided creating lesions in the subthalamic nucleus for fear of causing hemiballism, preliminary studies suggest that this procedure may be performed safely and may result in an improvement in parkinsonism.¹⁹⁰ The transplantation of autologous adrenal medulla to the striatum in an attempt to restore the deficient striatal dopaminergic innervation has been largely abandoned because of its lack of efficacy, which is related at least in part to the poor survival of the implanted adrenal tissue.¹⁹¹ Allogeneic transplantation of fetal mesencephalon is currently being stud-

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ied, and initial reports show promising results.¹⁹²⁻¹⁹⁴ Both positron-emission tomography^{198,199} and autopsy¹⁹⁴ studies have established the long-term viability of transplanted dopaminergic neurons. In part to overcome ethical issues and problems in obtaining adequate numbers of dopaminergic cells (at least three to four fetuses may be required per side, amounting to six or more fetuses per patient), investigators are studying xenotransplantation with use of embryonic porcine mesencephalon. Such studies have also shown that transplanted cells survive for several months.¹⁹⁷ Sufficient data on the safety and efficacy of the allografts and the xenografts have not yet been published.

Another approach currently under study is the intraventricular delivery of the dopaminergic neurotrophic factor GDNF.⁶³ A technique that may be applicable in the future is the implantation of foreign cells in semipermeable polymeric capsules, thus obviating the need for potentially harmful immunosuppressive therapy. This method would allow the bidirectional diffusion of such substances as neurotransmitters and nutrients but would prevent antigenic stimulation of host defenses and thus rejection.¹⁹⁸ However, the reinnervation and synaptic interactions that are possible with successful direct-transplantation techniques would not be possible with this therapy.

In the future, surgical interventions may incorporate advances in gene therapy. Gene transfer is being examined in animal models of parkinsonism in studies involving genetically manipulated implantable cells (so-called *ex vivo* techniques) or viral vectors (or the DNA of interest presented in some other fashion) directly injected into the brain (in *vivo* techniques). A third form of gene therapy is the modulation of the level of expression of a gene of interest within the brain — for example, with use of antisense oligonucleotides. The current objective¹⁹⁹ is to enhance the expression of enzymes in the biosynthetic pathway of dopamine (tyrosine hydroxylase, guanosine triphosphate cyclohydrolase, and aromatic L-amino acid decarboxylase) or neurotrophic factors (BDNF or GDNF). Genes coding for molecules that block apoptosis, scavenge free radicals, enhance the clearance of toxic metabolites, or improve mitochondrial function could also be considered. Issues of efficacy, safety, regulation of gene expression, and the limited long-term expression of foreign genes need to be addressed.

SUMMARY

At no time in the past have the basic and clinical sciences applied to Parkinson's disease been so active. Experimental therapies under study at present promise to improve on the limitations of existing treatments. Future progress in understanding the causation and pathogenesis of the disorder will per-

mit the development of new treatments that will slow, halt, or even reverse the currently inexorable progressive course of Parkinson's disease.

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